

REMARKS

Claims 1-55 are pending in the application. Claims 1, 18, and 34 have been amended and new claims 48-55 have been added. Support for the amendments and new claims can be found in the specification at, e.g., page 2, lines 15-18; page 4, lines 25-29; page 5, lines 1-3; page 13, lines 26-28; page 14, line 29, to page 15, line 16; page 29, lines 12-14; and page 33, lines 31-38. No new matter has been added by these amendments.

Claim Objections

At page 2 of the Office Action, claim 32 was objected to because of its use of the term "inclusive." It is applicants' understanding that this objection was intended to apply to claim 34. Claim 34 has been amended to delete the term "inclusive."

35 U.S.C. §103(a) (Obviousness)

At pages 3-6 of the Office Action, claims 1-4, 12-17, 19-25, and 32-46 were rejected as allegedly unpatentable over Shah, U.S. Patent No. 6,020,004, in view of Chen et al., U.S. Patent No. 6,537, 813 ("Chen") and Tice et al., U.S. Patent No. 4,389,330 ("Tice").

Applicants respectfully traverse the rejection in view of the claim amendments and the following remarks.

Independent claim 1 is directed to a process for preparing nucleic acid-containing microparticles. The method requires "continuous" action at the following steps (maintaining the lettering for the steps used in the claim): (b) continuously supplying a first emulsion to a mixing chamber; (c) continuously supplying a second aqueous solution to the mixing chamber; (d) continuously emulsifying the first emulsion and the second aqueous solution in the mixing chamber to form a second emulsion; and (e) continuously transferring the second emulsion from the mixing chamber to a solvent removal device. An aqueous suspension of nucleic acid-containing microparticles is ultimately formed in the solvent removal device in step (f) via diffusion of the organic solvent into an aqueous phase of the second emulsion. As noted in the specification, "a 'solvent removal device' is a device that accomplishes removal of the solvent

from microparticles, but not necessarily from the fluid in which they are suspended” (specification at page 4, lines 25-27).

As an initial matter, applicants respectfully contest the assertion at page 3 of the Office Action that “Shah teaches a continuous process for the preparation of 0.5 μ microparticles.” Shah describes in several passages the preparation of a “continuous phase” into which a mixture of an active ingredient and a polymer are dispersed. However, Shah nowhere describes or suggests the use of a “continuous process” for the preparation of microparticles.

Shah describes “an improved method for preparing polymeric microparticles containing an active ingredient through unique utilization of direct lyophilization of emulsion or suspension” (Shah at column 2, lines 56-59). The “direct lyophilization” methodology of Shah is used to remove aqueous and organic solvents and produce the microparticles (Shah at column 5, lines 63-65). According to Shah “[i]t is utilization of this single step, i.e., direct lyophilization of the final emulsion or suspension, which refines and simplifies the present process over previously described processes, which require multiple steps and are often cumbersome” (Shah at column 6, line 66, to column 7, line 3).

In addition to Shah’s failure to disclose or suggest a “continuous process” for the preparation of microparticles, Shah also differs from the claimed methods in that it does not describe or suggest transferring an emulsion to a solvent removal device or forming an aqueous suspension of nucleic acid-containing microparticles in a solvent removal device via diffusion of organic solvent into an aqueous phase of the emulsion.

Chen and Tice, the secondary references cited in the present rejection, do not add what is lacking in Shah and would not have led the person of ordinary skill in the art to modify the methods of Shah so as to result in the claimed invention.

Chen describes various methods and apparatuses for the preparation of gene therapeutic compositions as well as the compositions formed thereby. However, as noted at page 4 of the Office Action, “[n]either Shah, nor Chen et al. teach removing the organic solvent from the second emulsion to form an aqueous suspension of microcapsules (step “f” of claim 1).” As amended, step (f) of claim 1 is directed to “forming an aqueous suspension of nucleic acid-

containing microparticles in the solvent removal device via diffusion of the organic solvent into an aqueous phase of the second emulsion.”

Tice describes a multi-step process for the preparation of microcapsules. The “central feature” of Tice’s process “resides in the fact that during preparation solvent is removed from the microcapsules suspended in a fluid medium in two distinct steps rather than in one process step” (Tice at column 2, lines 14-18). In Tice’s first step, the organic solvent in the microdroplets in the organic solvent immiscible fluid is partially removed by techniques such as heating, the application of a reduced pressure, or a combination of both (Tice at column 4, lines 9-15). After Tice’s first stage of solvent removal, the dispersed microcapsules in the solvent immiscible fluid medium are isolated from the fluid medium by means of separation such as decanting or filtering (Tice at column 4, lines 24-31). In Tice’s second step, “the remainder of the solvent in the microcapsules is removed by extraction” (Tice at column 4, lines 32-42).

In contrast to Tice’s two-step solvent removal method, step (f) of claim 1 requires that an aqueous suspension of nucleic acid-containing microparticles is formed via diffusion of the organic solvent into an aqueous phase of the second emulsion. This formation of microparticles is accomplished by removal of the solvent from nascent microparticles (via diffusion into the surrounding aqueous phase), but not necessarily from the fluid in which they are suspended (*cf.* Tice, which removes solvent in the first step of its method via evaporation). Nothing in Tice (or Shah or Chen) suggests such a means of forming nucleic acid-containing microparticles.

In addition to the foregoing remarks, the person of ordinary skill in the art would have had no reason to combine selected steps from the distinct methods described in each of Shah, Chen, and Tice. The present rejection appears to rest, at least in part, on the assertion at page 5 of the Office Action that “it would have been obvious to one of skill in the art, at the time the invention was made, to further modify the method taught by the combined teachings of Shah and Chen et al. by removing the solvent using the two-step procedure of Tice et al.” However, as noted above, Shah places a clear emphasis on the importance of using only a single step (direct lyophilization) on the final emulsion or suspension (Shah at column 6, line 66 to column 7, line 3). Given this emphasis, the skilled person would not have sought to modify Shah by adding

more steps (i.e., Tice's two-step solvent removal) to the method. Adding the steps described in Tice would not only have been counter-indicated by Shah (which states that its single step method is advantageous over those that require multiple steps and are cumbersome), it is not clear where the solvent removal steps of Tice could even be applied in comparison to Shah's direct lyophilization step or what type of benefit (if any) such an addition might be expected to achieve over the direct lyophilization step of Shah. As a result, the skilled person would have had no reason to make the modifications to Shah, Chen, and Tice suggested in the Office Action.

In view of the foregoing remarks, applicants respectfully submit that the combination of Shah, Chen, and Tice do not render obvious the claimed methods. Applicants request that the Examiner withdraw the rejection of independent claim 1 and claims 2-4, 12-17, 19-25, and 32-46 that depend therefrom.

At pages 6-7 of the Office Action, claims 1-6, 12-17, 19-25, and 32-46 were rejected as allegedly unpatentable over Shah taken with Chen and Tice, as applied to claims 1-4, 12-17, 19-25, and 32-46 above, in further view of Parikh et al., U.S. Patent No. 5,660,858 ("Parikh").

The Office Action cited Parikh as describing the use of lipid stabilizers (recited in dependent claims 5 and 6) and asserted that "[i]t would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Shah taken with Chen et al. and Tice et al. by including lipid stabilizers".

As detailed above, the combination of Shah, Chen, and Tice does not render obvious the method of independent claim 1. Parikh provides nothing that supplements the deficiencies of Shah, Chen, and Tice or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 5 and 6 should also be in condition for allowance.

At pages 7-8 of the Office Action, claims 1-4 and 7-47 were rejected as allegedly unpatentable over Shah taken with Chen and Tice, as applied to claims 1-4, 12-17, 19-25, and

32-46 above, in further view of Hartounian et al., U.S. Published Application Number 20020039596 ("Hartounian") and Hedley et al., U.S. Patent No. 5,783,567 ("Hedley").

The Office Action cited Hartounian and Hedley as allegedly describing features of various dependent claims and asserted that it would have been obvious to modify the methods of Shah, Chen, and Tice in view of Hartounian and Hedley to arrive at the methods of these dependent claims.

As detailed above, the combination of Shah, Chen, and Tice does not render obvious the method of independent claim 1. Hartounian and Hedley provide nothing that supplements the deficiencies of Shah, Chen, and Tice or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, all of the remaining dependent claims should also be in condition for allowance.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance.

Enclosed is a Petition for Extension of Time. The extension of time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 08191-012002.

Respectfully submitted,

Date: June 14, 2007



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